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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,693	02/02/2001	Mike A. Clark	PHOE-0060	9010

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/28/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/775,693	CLARK ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7,27 and 31-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 6-7, 27, 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 1-2, 6-7, 27, 31-36 are examined in the instant application.

NEW REJECTION BASED ON THE AMENDMENT

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1-2, 27 are rejected under 35 USC 103(a) as being unpatentable over Clark (US 6,183,738 B1), in view of Sugimura et al, 1992 (Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01, of record), and Filpula et al (US 5,804,183, of record) , and further in view of O'brien, WE, 1979 (Biochemistry, 18(24): 5353-6, of record).

Claim 1 is drawn to: A method for identifying a cancer patient suffering from hepatoma or sarcoma who is susceptible to arginine deprivation therapy comprising the steps:

a) obtaining a hepatoma or sarcoma tumor sample from the cancer patient; and

b) detecting the presence or absence of argininosuccinate synthetase protein in said hepatoma or sarcoma tumor sample, wherein the absence of argininosuccinate

synthetase protein in said hepatoma or sarcoma tumor sample is indicative of a cancer patient who is a candidate for arginine deprivation therapy and the presence of argininosuccinate synthetase protein in said canccrcur, hepatoma or sarcoma tumor sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

Claim 2 is drawn to: The method of claim 1 wherein prior to, simultaneous with, or after testing the hepatoma or sarcoma tumor sample, the method further comprises the steps of:

c) obtaining a non-cancerous sample of the corresponding tissue from the cancer patient; and

d) detecting the presence or absence of argininosuccinate synthetase protein in said non-cancerous sample, wherein the absence of argininosuccinate synthetase protein in said non-cancerous sample and the absence of argininosuccinate synthetase protein in said hepatoma or sarcoma tumor sample is indicative of a cancer patient who is not a good candidate for arginine deprivation therapy, wherein the presence of argininosuccinate synthetase protein in said non-cancerous sample and the absence of argininosuccinate synthetase protein in said hepatoma or sarcoma tumor sample is indicative of a cancer patient who is a good candidate for arginine deprivation therapy, and wherein the presence of argininosuccinate synthetase protein in said hepatoma or sarcoma tumor sample is indicative of a cancer patient who is not a candidate for arginine deprivation therapy.

Claim 27 is drawn to the method of claim 1, wherein the detection of argininosuccinate synthetase protein is by an antibody specific for said protein, or portion thereof.

Clark teaches a complete **correlation** between the **sensitivity to ADI** treatment and an inability to express the enzyme arginosuccinate synthetase **(ASS),** as shown by measuring the

level of mRNA of the enzyme in treated cancer cells in vitro, such as **sarcoma, hepatoma**, melanoma (column 10, lines 54-58, Example 4 and table 1 on column 10). Clark teaches that ADI toxicity results from inability to induce arginosuccinate synthetase, and therefore, these cells cannot synthesize arginine from citrulline, and are unable to synthesize the protein necessary for growth (column 10, paragraph under Table 1). Clark teaches that in tissue culture, 64% sarcoma and 100% hepatoma are inhibited by treatment with arginine deiminase (ADI) (Example 4 and table 1 on column 10). Clark teaches that in nude mice, heptoma are successfully treated with ADI (Example 8 on column 12, and figure 9).

Clark does not teach a method for identifying a cancer patient suffering from hepatoma or sarcoma who is susceptible to arginine deprivation therapy, comprising detecting arginosuccinate synthetase (ASS) protein, wherein the absence of ASS in the hepatoma or sarcoma sample from said patient is indicative that the patient is a candidate for arginine deprivation therapy.

Sugimura et al teach that arginine deiminase (AD) is a potent inhibitor for some but not all tumor cell lines in vitro (abstract). Further, from the following teaching of Sugimura et al (Sugimura et al, abstract, p.194, second column, first paragraph under "Discussion"), one would have concluded that **high sensitivity to AD treatment correlates with the absence or low level of the enzyme arginosuccinate synthetase (ASS)** gene expression, thus collaborating the teaching of Clark. Sugimura et al teach that among the five melanoma cell lines tested that are sensitive to AD treatment, the enzyme arginosuccinate synthetase (ASS) gene expression, as detected by PCR, is also reduced, being almost absent in four cell lines, and at low level in one cell line G361 (abstract, p.192, first column, second paragraph). It is noted that the melanoma cell line G361, having a relatively higher level of ASS expression than the other four melanoma

cell lines (1/5 fold lower ASS than that of the control TL-Mor, Sugimura et al, p. 194, second column, first paragraph), although is still sensitive to AD, however, the level of its sensitivity to AD treatment is much less than that of the other four melanoma cells, that do not have ASS or have lower level of ASS (A375 has 1/34 fold lower than that of the control TL-Mor, Sugimura et al, p. 194, first column, last paragraph). That is, the melanoma cell line G361 requires a much higher level of concentration of AD, shows "a marginal response" , i.e. a reduction to 23% of control cell proliferation at 130 ng/ml of AD, as compared to a level of 16 ng/ml, or 32 ng/ml of AD, which AD level almost completely inhibits cell proliferation of the other four melanoma cell lines (Sugimura et al, p.193, first column, paragraph before last). It is further noted that the Hela epithelial carcinoma cell line, having even a higher level of ASS than the marginal melanoma cell line G361 (1/3 fold lower versus 1/5 lower than that of the control TL-Mor) is not sensitive to AD treatment (figure 4 and p.194, second column, first paragraph), thus confirming a correlation between the level of ASS and sensitivity to AD treatment. In other word, the higher the level of ASS, the less sensitivity to AD treatment, and that at the ASS level of Hela cells, at 1/3 fold less than that of the control cells, one do not see sensitivity to AD treatment. This correlation between sensitivity of AD treatment and low level of ASS gene expression is found not only in the melanoma cell lines, but is found as well in blood peripheral lymphocytes that are sensitive to AD, as confirmed by the teaching of Sugimura et al that the blood peripheral lymphocytes that are sensitive to AD, "because" they have extremely low level of ASS (Sugimura et al, p.191, second column, last four lines bridging p.192). In addition, Sugimura et al teach that melanoma cell lines have high sensitivity to AD treatment, because of their inability

to utilize C-citrulline, which is converted to arginine by the enzyme ASS, which arginine is essential for survival of many mammalian cells (p.191, second column, bridging p.192).

Filpula et al teach treating of carcinoma that are deficient in ASS, and melanoma, using AD (claims 7-10). US 5,804,183 teaches a method for reducing the level of arginine comprising administering arginine deaminase (AD) (claim 5). In other words, treating with AD, which reduces the level of arginine, is the same as arginine deprivation therapy.

O'brien teaches detection of argininosuccinate synthetase in human liver, using an antibody specific for argininosuccinate synthetase, by electrophoresis analysis.

It would have been prima facia obvious for one of ordinary skill in the art at the time the invention was made to screen for **human** cancer patients, including those suffering from hepatoma or sarcoma, that are deficient in arginosuccinate synthetase (ASS) to increase the efficiency of AD cancer therapy, because of the following reasons:

1) The absence or low level of ASS in several cancer cells in vitro, including hepatoma and sarcoma, is correlated with susceptibility to AD treatment, in view of the teaching of Clark, and Sugimura et al.

2) The enzyme ASS is crucial for the synthesis of arginine, the presence of which is essential for cell survival as taught by Sugimura et al, and Clark. Thus one would have expected that absence or low level of the enzyme ASS, resulting in low level of synthesized arginine in cells, would make the cells susceptible to further arginine depletion by AD treatment.

Further, it would have been obvious to detect the ASS protein, using the antibody specific for said protein, as taught by O'brien et al, in addition to detect the mRNA level, as taught by

Clark or Sugimura et al, to expand the versatility of the method to identify cancer patients that are susceptible to AD treatment.

One would have a reasonable expectation of success because of the following reasons:

1) Hepatoma cells, that show a negative correlation with the level of ASS, are susceptible to AD treatment in nude mice, in view of the teaching of Clark. Similarly, successful treating cancers that are deficient in ASS, such as carcinoma and melonama is taught by Filpula et al.

2) Further, although Clark and Sugimura et al only teach that the level of ASS gene expression is detected by PCR, or Northern blot, the absence of ASS RNA taught by Sugimura et al, or Clark et al would correlate with the absence of ASS protein.

2. Claims 6-7, 31-32, 35-36 are rejected under 35 USC 103(a) as being unpatentable over Clark (US 6,183,738 B1), in view of Sugimura, K, et al, 1992, Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01, Filpula et al (US 5,804,183, filed on 01/31/97), and O'brien, WE, 1979 (Biochemistry, 18(24): 5353-6), supra, and further in view of Thompson (US 5,424,192, of record).

Claim 6-7 are drawn to the method of claim 1, using Western blot, ELISA, enzyme assays, slot blotting, electrophoresis, or immunochemistry.

Claims 31-32, 35-36 are drawn to the method of claim 27, wherein the antibody has a detectable label (claim 31), which is radioactive, fluorescent or chromomorphic (claim 32), or an enzyme (claim 35) or has a visible color (claim 36).

The teaching of Clark, Sugimura et al, Filpula et al, and O'brien has been set forth above.

Clark, Sugimura et al, Filpula et al, and O'brien do not teach detection of ASS by an antibody specific for said protein, using Western blot, ELISA, enzyme assay, slot blotting, or

immunochemistry, wherein the antibody is labeled with radioactive, fluorescent or chromophomorphic label, or an enzyme, or has a visible color.

Thompson et al teach a method for detecting prostate cancer, which is an EIA, ELISA, a Western blot, a slot blot, or an IRA (see claim 12), using an antibody that is labeled with a detectable label, such as a radioisotope, a fluorescent chemical, an enzyme, a chromatic chemical (see claim 29).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to use Western blot, ELISA, enzyme immunoassays, or slot blotting, as taught by Thompson et al, besides electrophoresis taught by O'brien for detecting argininosuccinate synthetase protein, wherein the antibody taught by O'brien is labeled with a radioisotope, a fluorescent chemical, an enzyme, or a chromatic chemical, using the method taught by Thompson et al, to increase the versatility of the method to identify cancer patients that are susceptible to AD treatment.

3. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Clark (US 6,183,738 B1), in view of Sugimura, K, et al, 1992, Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01, Filpula et al (US 5,804,183, filed on 01/31/97), and O'brien, WE, 1979 (Biochemistry, 18(24): 5353-6), supra, and further in view of Diamandis et al (US 6,068,830, having its PCT filed on 07/14/1994, of record).

Claim 33 is drawn to the method of claim 31, wherein said detectable label is I^{131}, I^{125}, C^{14}, S^{35}, P^{32}, or P^{33}.

The teaching of Clark, Sugimura et al, Filpula, and O'brien has been set forth above.

Clark, Sugimura et al, Filpula and O'brien do not teach that argininosuccinate synthetase protein is detected by an antibody, which is labeled with I^{131}, I^{125}, C^{14}, S^{35}, P^{32}, or P^{33}.

Diamandis et al teach a method for imaging cancer, using an antibody that is labeled with a radioisotope, wherein said radioisotope includes I^{131}, I^{125}, C^{14}, S^{35}, P^{32}, or P^{33} (claim 4).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to detect argininosuccinate synthetase protein, using the antibody taught by O'brien, wherein the antibody is labeled with a radioisotope, such as I^{131}, I^{125}, C^{14}, S^{35}, P^{32}, or P^{33}, as taught by Diamandis et al, to increase the versatility of the method to identify cancer patients that are susceptible to AD treatment.

4. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Clark (US 6,183,738 B1), in view of Sugimura, K, et al, 1992, Melanoma Res, 2: 191-196, IDS# AK, in paper No:6, on 06/19/01, Filpula et al (US 5,804,183, filed on 01/31/97), and O'brien, WE, 1979 (Biochemistry, 18(24): 5353-6), supra), and further in view of Wallace et al (US 6,124,106, filed on 03/10/99, of record) and Hansen et al, 1989 (Electrophoresis, 10 (8-9): 645-52, of record).

Claim 34 is drawn to the method of claim 31, wherein said detectable label is fluorescein, phycolipoprotein, or tetrarhodamine isothiocyanate.

The teaching of Clark, Sugimura et al, Filpula et al, and O'brien has been set forth above.

Clark, Sugimura et al, Filpula and O'brien do not teach that argininosuccinate synthetase protein is detected by an antibody that is labeled with fluorescein, phycolipoprotein, or tetraethyl rhodamine.

Wallace et al teach a method for detecting cancer, using an antibody that is labeled with fluorescein, phycolipoprotein, or tetraethyl rhodamine (see claim 10).

Hansen et al teach dectection of human lymphocytes, using tetrarhodamine isothiocyanate-labeled anti-IgG (abstract).

It would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made to detect argininosuccinate synthetase protein, using the antibody taught by O'brien, wherein the antibody is labeled with fluorescein, or phycolipoprotein, as taught by Wallace et al, or labeled with tetrarhodamine isothiocyanate, as taught by Hansen et al to increase the versatility of the method to identify cancer patients that are susceptible to AD treatment.

Answer to Applicant Response

The response asserts that the previous references do not teach or suggest that the level of ASS protein expressed in hepatoma or sarcoma could be used to predict whether the hepatomas and sarcomas would be sensitive to arginine deprivation therapy.

The response has been considered but is not found to be persuasive for the following reasons:

The new reference, Clark (US 6,183,738 B1) teaches that the level of ASS mRNAs expressed in hepatoma or sarcoma is correlated with sensitivity to arginine deprivation therapy (see new 103 rejections above).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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December 15, 2006

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